L Number	Hits	Search Text	DB	Time stamp
1	33	Morin NEAR Gregg	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/02/19 14:23
2	16	(Morin NEAR Gregg) and (mouse SAME telomerase)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/02/19 14:24
3	102	(mouse WITH telomerase) and (mutation mutant delete deletion knockout)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/02/19 14:25
4	253	telomerase NEAR reverse NEAR transcriptase	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/02/19 14:25
5	4	Allsopp NEAR richard	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/02/19 14:26
-	10	(("6284477") or ("6287839") or ("6291220") or ("6297356") or ("6297367")).PN.	USPAT; US-PGPUB; EPO; JPO; DERWENT; USOCR	2004/02/19 14:20
-	2	wo NEAR "9735967"	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/06 17:02
-	9	mouse WITH telomerase SAME (mutation mutant delete deletion knockout)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/06 17:05
-	86	mouse WITH telomerase	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/02/11 10:33
-	15	(US-6297356-$ or US-6297367-$ or US-6284477-$ or US-6291220-$ or US-5629154-$ or US-5643890-$ or US-5645986-$ or US-5695932-$).did. or (WO-9735967-$).did. or (US-6297367-$ or US-6245338-$ or US-5948664-$ or US-6297356-$ or US-6287839-$ or US-5583016-$).did.	USPAT; EPO; DERWENT	2003/02/06 17:09
-	17	GReider NEAR carol	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/06 17:16
-	12	(GReider NEAR carol) and mouse	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/06 17:16
-	195	(telomerase NEAR reverse NEAR transcriptase) AND (muta$5 dele$5 add$5 subst$5)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/02/11 10:39
-	16	((telomerase NEAR reverse NEAR transcriptase) AND (muta$5 dele$5 add$5 subst$5)) and mTERT	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/02/11 10:38
-	53	(telomerase NEAR reverse NEAR transcriptase) AND (muta$5 dele$5 add$5 subst$5).clm.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/02/11 10:40

```
=> d his

     (FILE 'HOME' ENTERED AT 11:15:17 ON 11 FEB 2004)

     FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED
     AT 11:15:25 ON 11 FEB 2004
L1          2697 S TELOMERASE REVERSE TRANSCRIPTASE
L2           180 S L1 AND LACK?
L3            50 S L2 AND (MOUSE OR MICE)
L4            30 DUP REM L3 (20 DUPLICATES REMOVED)
L5             0 S L4 AND PY<=1997
L6            30 FOCUS L4 1-
L7            28 S L1 AND KNOCKOUT
L8            17 DUP REM L7 (11 DUPLICATES REMOVED)
L9            17 SORT L8 PY

=> d an ti so au'ab pi l9 1-17

L9   ANSWER 1 OF 17      MEDLINE on STN
AN   1998022648      MEDLINE
TI   The end replication problem: more than one solution.
SO   NATURE MEDICINE, (1997 Nov) 3 (11) 1198-9.
     Journal code: 9502015. ISSN: 1078-8956.
AU   Lundblad V

L9   ANSWER 2 OF 17      MEDLINE on STN
AN   1998282105      MEDLINE
TI   Severe growth defect in mouse cells lacking the telomerase RNA component.
SO   NATURE GENETICS, (1998 Jun) 19 (2) 203-6.
     Journal code: 9216904. ISSN: 1061-4036.
AU   Niida H; Matsumoto T; Satoh H; Shiwa M; Tokutake Y; Furuichi Y; Shinkai Y
AB   The ribonucleoprotein enzyme telomerase synthesizes telomeric DNA onto
     chromosome ends. Telomere length is maintained, by the presence of
     telomerase activity, in the vast majority of primary tumours and stem
     cells, suggesting that telomere maintenance is essential for cellular
     immortalization. Recently, the telomerase RNA component in human and
     mouse (TERC and Terc, respectively), a telomerase-associated protein
     TEP1/TLP1 (refs 6,7) and the human catalytic subunit protein TERT (refs
     8,9) have been identified. To examine the role of telomerase in telomere
     maintenance and cellular viability, we established Terc-deficient
     embryonic stem (ES) cells. It is known that telomerase activity is absent
     in cells from Terc-knockout mice. Although the study showed
     that telomere shortening was observed in the Terc-deficient cells from
     first to six generation animals, whether telomerase-dependent telomere
     maintenance was essential for cellular viability remained to be
     elucidated. To address this issue, we examined Terc-deficient ES cells
     under long-term culture conditions. Accompanying the continual telomere
     shortening, the growth rate of Terc-deficient ES cells was gradually
     reduced after more than 300 divisions. An impaired growth rate was
     maintained to approximately 450 divisions, and then cell growth virtually
     stopped. These data clearly show that telomerase-dependent telomere
     maintenance is critical for the growth of mammalian cells.

L9   ANSWER 3 OF 17  CAPLUS  COPYRIGHT 2004 ACS on STN
AN   1998:221109  CAPLUS
DN   128:305676
TI   Telomerase reverse transcriptases of
     protozoa, yeasts and humans and conserved sequence motifs in the enzyme
SO   PCT Int. Appl., 312 pp.
     CODEN: PIXXD2
IN   Cech, Thomas R.; Lingner, Joachim; Nakamura, Toru; Chapman, Karen B.;
     Morin, Gregg B.; Harley, Calvin B.; Andrews, William H.
AB   The 123 kDa and 43 kDa subunits of the telomerase of Euplotes aediculatus,
     and related sequences from Schizosaccharomyces, Saccharomyces sequences,
     and human are characterized and genes and cDNAs encoding them are cloned.
     Conserved sequence features of the subunits are identified for use in the
     development of probes and primers for detection of telomerase genes in
     other organisms.
```

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9814592	A2	19980409	WO 1997-US17618	19971001
	WO 9814592	A3	19990401		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, US, US, US, US, US, US, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 6093809	A	20000725	US 1997-851843	19970506
	US 6261836	B1	20010717	US 1997-854050	19970509
	US 6475789	B1	20021105	US 1997-912951	19970814
	AU 9748036	A1	19980424	AU 1997-48036	19971001
	EP 932686	A2	19990804	EP 1997-910737	19971001
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	BR 9711844	A	20000118	BR 1997-11844	19971001
	JP 2001523947	T2	20011127	JP 1998-516802	19971001
	US 6166178	A	20001226	US 1997-974549	19971119
	US 6444650	B1	20020903	US 1998-52919	19980331
	MX 9902841	A	20000331	MX 1999-2841	19990325
	AU 763956	B2	20030807	AU 2001-47992	20010523
	US 2002173476	A1	20021121	US 2001-953052	20010914
	US 6627619	B2	20030930		

L9 ANSWER 4 OF 17 MEDLINE on STN

AN 2000051030 MEDLINE

TI Presence of telomeric G-strand tails in the telomerase catalytic subunit TERT **knockout** mice.

SO GENES TO CELLS, (1999 Oct) 4 (10) 563-72.
Journal code: 9607379. ISSN: 1356-9597.

AU Yuan X; Ishibashi S; Hatakeyama S; Saito M; Nakayama J; Nikaido R; Haruyama T; Watanabe Y; Iwata H; Iida M; Sugimura H; Yamada N; Ishikawa F

AB BACKGROUND: Telomerase consists of two essential subunits, the template RNA (TR; telomerase RNA) and the catalytic subunit TERT (**telomerase reverse transcriptase**).
Knockout mice with a mTR (mouse TR) deletion have been described and well characterized. However, mice with a mTERT (mouse TERT) deletion have not been reported. RESULTS: mTERT-**knockout** mice have been constructed. The first generation mTERT -/- mice were fertile, and did not show any noticeable macroscopic or microscopic phenotypic change. All tissue cells derived from mTERT -/- mice that were examined lacked telomerase activity, indicating that mTERT is the only gene encoding the telomerase catalytic subunit. Pulse field gel electrophoresis (PFGE) and nondenaturing in-gel hybridization analyses showed that mouse telomeric DNA has G-strand 5'-overhangs, as demonstrated for human and yeast cells. This telomeric single-stranded G-tail was also observed in MEF (mouse embryonic fibroblast) and liver cells derived from mTERT -/- mice. CONCLUSIONS: mTERT-**knockout** mice show phenotypes that are apparently normal at least during the early generations. This observation is similar to that obtained with the mTR-**knockout** mice. The presence of the telomeric G-strand tails in mTERT -/- mice suggests that these telomeric 5'-overhangs are produced by telomerase-independent mechanisms, as has been proposed for yeast and human.

> d his

(FILE 'HOME' ENTERED AT 11:15:17 ON 11 FEB 2004)

FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED AT 11:15:25 ON 11 FEB 2004

L1 2697 S TELOMERASE REVERSE TRANSCRIPTASE
L2 180 S L1 AND LACK?
L3 50 S L2 AND (MOUSE OR MICE)
L4 30 DUP REM L3 (20 DUPLICATES REMOVED)
L5 0 S L4 AND PY<=1997
L6 30 FOCUS L4 1-

=> d an ti so au ab l6 4 5 10 11 21

L6 ANSWER 4 OF 30 MEDLINE on STN
AN 2000051030 MEDLINE
TI Presence of telomeric G-strand tails in the telomerase catalytic subunit TERT knockout **mice**.
SO GENES TO CELLS, (1999 Oct) 4 (10) 563-72.
Journal code: 9607379. ISSN: 1356-9597.
AU Yuan X; Ishibashi S; Hatakeyama S; Saito M; Nakayama J; Nikaido R; Haruyama T; Watanabe Y; Iwata H; Iida M; Sugimura H; Yamada N; Ishikawa F
AB BACKGROUND: Telomerase consists of two essential subunits, the template RNA (TR; telomerase RNA) and the catalytic subunit TERT (**telomerase reverse transcriptase**). Knockout **mice** with a mTR (**mouse** TR) deletion have been described and well characterized. However, **mice** with a mTERT (**mouse** TERT) deletion have not been reported. RESULTS: mTERT-knockout **mice** have been constructed. The first generation mTERT -/- **mice** were fertile, and did not show any noticeable macroscopic or microscopic phenotypic change. All tissue cells derived from mTERT -/- **mice** that were examined **lacked** telomerase activity, indicating that mTERT is the only gene encoding the telomerase catalytic subunit. Pulse field gel electrophoresis (PFGE) and nondenaturing in-gel hybridization analyses showed that **mouse** telomeric DNA has G-strand 5'-overhangs, as demonstrated for human and yeast cells. This telomeric single-stranded G-tail was also observed in MEF (**mouse** embryonic fibroblast) and liver cells derived from mTERT -/- **mice**. CONCLUSIONS: mTERT-knockout **mice** show phenotypes that are apparently normal at least during the early generations. This observation is similar to that obtained with the mTR-knockout **mice**. The presence of the telomeric G-strand tails in mTERT -/- **mice** suggests that these telomeric 5'-overhangs are produced by telomerase-independent mechanisms, as has been proposed for yeast and human.

L6 ANSWER 5 OF 30 MEDLINE on STN
AN 2002172341 MEDLINE
TI Preferential maintenance of critically short telomeres in mammalian cells heterozygous for mTert.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2002 Mar 19) 99 (6) 3597-602.
Journal code: 7505876. ISSN: 0027-8424.
AU Liu Yie; Kha Hue; Ungrin Mark; Robinson Murray O; Harrington Lea
AB Prolonged growth of murine embryonic stem (ES) cells **lacking** the **telomerase reverse transcriptase**, mTert, results in a loss of telomere DNA and an increased incidence of end-to-end fusions and aneuploidy. Furthermore, loss of only one copy of mTert also results in telomere shortening intermediate between wild-type (wt) and mTert-null ES cells [Liu, Y., Snow, B. E., Hande, M. P., Yeung, D., Erdmann, N. J., Wakeham, A., Itie, A., Siderovski, D. P., Lansdorp, P. M., Robinson, M. O. & Harrington, L. (2000) Curr. Biol. 10, 1459-1462]. Unexpectedly, although average telomere length in mTert(+/-) ES cells declined to a similar level as mTert-null ES cells, mTert(+/-) ES cell lines retained a minimal telomeric DNA signal at all chromosome ends. Consequently, no end-to-end fusions and genome instability were observed in the latest passages of mTert(+/-) ES cell lines. These data uncover a functional distinction between the dosage-dependent function of telomerase

in average telomere-length maintenance and the selective maintenance of critically short telomeres in cells heterozygous for mTert. In normal and tumor cells, we suggest that telomerase activity insufficient to maintain a given average telomere length may, nonetheless, provide a protective advantage from end-to-end fusion and genome instability.

L6 ANSWER 10 OF 30 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
AN 2003:304476 SCISEARCH
TI Deletion of the **telomerase reverse transcriptase** gene and haploinsufficiency of telomere maintenance in Cri du chat syndrome
SO AMERICAN JOURNAL OF HUMAN GENETICS, (APR 2003) Vol. 72, No. 4, pp. 940-948.
Publisher: UNIV CHICAGO PRESS, 1427 E 60TH ST, CHICAGO, IL 60637-2954 USA.
ISSN: 0002-9297.
AU Zhang A J; Zheng C Y; Hou M; Lindvall C; Li K J; Erlandsson F; Bjorkholm M; Gruber A; Blennow E; Xu D W (Reprint)
AB Cri du chat syndrome (CdCS) results from loss of the distal portion of chromosome 5p, where the **telomerase reverse transcriptase** (hTERT) gene is localized (5p15.33). hTERT is the rate-limiting component for telomerase activity that is essential for telomere-length maintenance and sustained cell proliferation. Here, we show that a concomitant deletion of the hTERT allele occurs in all 10 patients with CdCS whom we examined. Induction of hTERT mRNA in proliferating lymphocytes derived from five of seven patients was lower than that in unaffected control individuals ($P < .05$). The patient lymphocytes exhibited shorter telomeres than age-matched unaffected individuals ($P < .0001$). A reduction in replicative life span and a high rate of chromosome fusions were observed in cultured patient fibroblasts. Reconstitution of telomerase activity by ectopic expression of hTERT extended the telomere length, increased the population doublings, and prevented the end-to-end fusion of chromosomes. We conclude that hTERT is limiting and haploinsufficient for telomere maintenance in humans in vivo. Accordingly, the hTERT deletion may be one genetic element contributing to the phenotypic changes in CdCS.

L6 ANSWER 11 OF 30 MEDLINE on STN
AN 2001040123 MEDLINE
TI Telomerase-associated protein TEP1 is not essential for telomerase activity or telomere length maintenance in vivo.
SO MOLECULAR AND CELLULAR BIOLOGY, (2000 Nov) 20 (21) 8178-84.
Journal code: 8109087. ISSN: 0270-7306.
AU Liu Y; Snow B E; Hande M P; Baerlocher G; Kickhoefer V A; Yeung D; Wakeham A; Itie A; Siderovski D P; Lansdorp P M; Robinson M O; Harrington L
AB TEP1 is a mammalian telomerase-associated protein with similarity to the Tetrahymena telomerase protein p80. Like p80, TEP1 is associated with telomerase activity and the **telomerase reverse transcriptase**, and it specifically interacts with the telomerase RNA. To determine the role of mTep1 in telomerase function in vivo, we generated **mouse** embryonic stem (ES) cells and **mice lacking** mTep1. The mTep1-deficient (mTep1(-/-)) **mice** were viable and were bred for seven successive generations with no obvious phenotypic abnormalities. All murine tissues from mTep1(-/-) **mice** possessed a level of telomerase activity comparable to that in wild-type **mice**. In addition, analysis of several tissues that normally **lack** telomerase activity revealed no reactivation of telomerase activity in mTep1(-/-) **mice**. Telomere length, even in later generations of mTep1(-/-) **mice**, was equivalent to that in wild-type animals. ES cells deficient in mTep1 also showed no detectable alteration in telomerase activity or telomere length with increased passage in culture. Thus, mTep1 appears to be completely dispensable for telomerase function in vivo. Recently, TEP1 has been identified within a second ribonucleoprotein (RNP) complex, the vault particle. TEP1 can also specifically bind to a small RNA, vRNA, which is associated with the vault particle and is unrelated in sequence to mammalian telomerase RNA. These results reveal that TEP1 is an RNA binding protein that is not restricted to the telomerase complex and that TEP1 plays a redundant role in the assembly or localization of the telomerase RNP in vivo.

L6 ANSWER 21 OF 30 MEDLINE on STN
AN 1998282105 MEDLINE
TI Severe growth defect in **mouse** cells **lacking** the telomerase RNA component.
SO NATURE GENETICS, (1998 Jun) 19 (2) 203-6.
Journal code: 9216904. ISSN: 1061-4036.
AU Niida H; Matsumoto T; Satoh H; Shiwa M; Tokutake Y; Furuichi Y; Shinkai Y
AB The ribonucleoprotein enzyme telomerase synthesizes telomeric DNA onto chromosome ends. Telomere length is maintained, by the presence of telomerase activity, in the vast majority of primary tumours and stem cells, suggesting that telomere maintenance is essential for cellular immortalization. Recently, the telomerase RNA component in human and **mouse** (TERC and Terc, respectively), a telomerase-associated protein TEP1/TLP1 (refs 6,7) and the human catalytic subunit protein TERT (refs 8,9) have been identified. To examine the role of telomerase in telomere maintenance and cellular viability, we established Terc-deficient embryonic stem (ES) cells. It is known that telomerase activity is absent in cells from Terc-knockout **mice**. Although the study showed that telomere shortening was observed in the Terc-deficient cells from first to six generation animals, whether telomerase-dependent telomere maintenance was essential for cellular viability remained to be elucidated. To address this issue, we examined Terc-deficient ES cells under long-term culture conditions. Accompanying the continual telomere shortening, the growth rate of Terc-deficient ES cells was gradually reduced after more than 300 divisions. An impaired growth rate was maintained to approximately 450 divisions, and then cell growth virtually stopped. These data clearly show that telomerase-dependent telomere maintenance is critical for the growth of mammalian cells.

L9 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:736388 CAPLUS
DN 137:258522
TI Use of **telomerase reverse transcriptase** to create homozygous **knockout** animals
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
IN Clark, A. John; Denning, Chris; Cui, Wei; Zhao, Debbiao
AB This disclosure provides a system for creating cloned cells and embryos that are genetically modified. Cells are treated to increase expression of telomerase and potentially extend replicative capacity and improve their genetic stability. One or more genetic modifications is made to inactivate a gene or confer desirable features, growing and selecting the cells as needed. The modified nucleus can then be transferred to a suitable recipient cell, which can then be used to grow an embryo with the conferred attributes. The method is exemplified by increasing TERT (or TRT, for **telomerase reverse transcriptase**) activity in sheep or pig nuclear donor cells by transforming human TERT gene. The prion protein PrP or a[1,3] galactosyltransferase gene are targeted to be knocked out in telomerized sheep fetal fibroblast cell line. Gene **knockout** and telomerizing fibroblasts can be done simultaneously. This technol. makes it possible to create embryos, animals and embryonic cell lines with multiple genetic modifications, including homozygously inactivated genes and gene substitutions.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002074935	A2	20020926	WO 2002-GB1364	20020321
	WO 2002074935	A3	20030313		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2003068818	A1	20030410	US 2002-105963	20020321
	US 2003175967	A1	20030918	US 2002-105616	20020321

L6 ANSWER 4 OF 30 MEDLINE on STN
AN 2000051030 MEDLINE
TI Presence of telomeric G-strand tails in the telomerase catalytic subunit TERT knockout **mice**.
SO GENES TO CELLS, (1999 Oct) 4 (10) 563-72.
Journal code: 9607379. ISSN: 1356-9597.
AU Yuan X; Ishibashi S; Hatakeyama S; Saito M; Nakayama J; Nikaido R; Haruyama T; Watanabe Y; Iwata H; Iida M; Sugimura H; Yamada N; Ishikawa F
AB BACKGROUND: Telomerase consists of two essential subunits, the template RNA (TR; telomerase RNA) and the catalytic subunit TERT (**telomerase reverse transcriptase**). Knockout **mice** with a mTR (**mouse** TR) deletion have been described and well characterized. However, **mice** with a mTERT (**mouse** TERT) deletion have not been reported. RESULTS: mTERT-knockout **mice** have been constructed. The first generation mTERT -/- **mice** were fertile, and did not show any noticeable macroscopic or microscopic phenotypic change. All tissue cells derived from mTERT -/- **mice** that were examined **lacked** telomerase activity, indicating that mTERT is the only gene encoding the telomerase catalytic subunit. Pulse field gel electrophoresis (PFGE) and nondenaturing in-gel hybridization analyses showed that **mouse** telomeric DNA has G-strand 5'-overhangs, as demonstrated for human and yeast cells. This telomeric single-stranded G-tail was also observed in MEF (**mouse** embryonic fibroblast) and liver cells derived from mTERT -/- **mice**. CONCLUSIONS: mTERT-knockout **mice** show phenotypes that are apparently normal at least during the early generations. This observation is similar to that obtained with the mTR-knockout **mice**. The presence of the telomeric G-strand tails in mTERT -/- **mice** suggests that these telomeric 5'-overhangs are produced by telomerase-independent mechanisms, as has been proposed for yeast and human.

(FILE 'HOME' ENTERED AT 10:04:29 ON 11 FEB 2004)

FILE 'MEDLINE, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED AT 10:04:48 ON 11 FEB 2004

L1 3744 S (TELOMERASE REVERSE TRANSCRIPTASE) OR HTERT OR MTERT
L2 1587 S L1 AND (MUTA? OR DEL? OR SUBS? OR ADD?)
L3 17 S L2 AND PY<=1997
L4 17 SORT L3 PY
L5 10 DUP REM L4 (7 DUPLICATES REMOVED)

=> d an ti so au ab pi l5 1-10

L5 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:241907 CAPLUS
DN 138:251121
TI Retinal cell lines with extended life-span and their applications
SO U.S. Pat. Appl. Publ., 55 pp., Cont.-in-part of U.S. 6,090,624.
CODEN: USXXCO
IN Greenwood, John; Adamson, Peter; Lund, Raymond
AB The invention features retina-derived (retinal endothelial or retinal epithelial pigment) cell lines with extended life-span and capable of being implanted in the retina and of carrying a therapeutic **substance** to the eye and to the central nervous system. Such lines can also be used as a model for studying blood/central nervous system interfaces. These lines are derived from primary retinal cultures selected from the group consisting of primary retinal endothelial cells and primary retinal epithelial cells, comprise a polynucleotide containing an oncogene, which polynucleotide is optionally associated with at least one selection gene, and have the morphol. characteristics and at least the expression characteristics of the surface antigens of corresponding primary cultures.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI US 2003059868	A1	20030327	US 2000-559707	20000427	
FR 2747690	A1	19971024	FR 1996-4964	19960419	<--
FR 2747690	B1	19980612			
WO 9740139	A1	19971030	WO 1997-FR709	19970418	<--
W: AU, CA, JP, NZ, US					
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
US 6183735	B1	20010206	US 1998-973553	19980122	
US 6090624	A	20000718	US 1998-182516	19981030	
WO 2001081551	A2	20011101	WO 2001-IB860	20010427	
WO 2001081551	A3	20021017			
WO 2001081551	C1	20030103			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
EP 1287115	A2	20030305	EP 2001-931995	20010427	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2003530880	T2	20031021	JP 2001-578622	20010427	

L5 ANSWER 2 OF 10 MEDLINE on STN DUPLICATE 1
AN 1998022648 MEDLINE
TI The end replication problem: more than one solution.
SO NATURE MEDICINE, **(1997 Nov)** 3 (11) 1198-9.
Journal code: 9502015. ISSN: 1078-8956.
AU Lundblad V

L5 ANSWER 3 OF 10 MEDLINE on STN DUPLICATE 2
AN 1998051184 MEDLINE
TI Human telomerase contains evolutionarily conserved catalytic and

structural subunits.
SO GENES AND DEVELOPMENT, **(1997 Dec 1)** 11 (23) 3109-15.
Journal code: 8711660. ISSN: 0890-9369.
AU Harrington L; Zhou W; McPhail T; Oulton R; Yeung D S; Mar V; Bass M B; Robinson M O
AB We have cloned and characterized a human gene encoding TP2 (telomerase-associated protein 2), a protein with similarity to reverse transcriptases and the catalytic telomerase subunits from Saccharomyces cerevisiae and Euplotes aediculatus. Indirect immunofluorescence revealed that TP2 was localized to the nucleus. Using antibodies to endogenous and epitope-tagged TP2, we found that TP2 was associated specifically with human telomerase activity and the recently identified telomerase-associated protein TP1. **Mutation** of conserved residues within the reverse transcriptase domain of TP2 severely reduced associated telomerase activity. These results suggest that telomerase is an evolutionarily conserved multisubunit complex composed of both structural and catalytic subunits.

L5 ANSWER 4 OF 10 MEDLINE on STN DUPLICATE 3
AN 1998083979 MEDLINE
TI Telomere and telomerase associated genes.
SO GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], **(1997 Dec)** 24 (15) 2196-201.
Journal code: 7810034. ISSN: 0385-0684.
AU Tahara H; Tahara E; Tahara E; Ide T
AB Telomerase is a ribonucleoprotein, telomere specific reverse transcriptase, which contains some protein components and telomerase RNA components. Human telomerase RNA and some telomerase components have been identified but not completely. More recently, human telomerase catarytic subunits have been cloned, which are called hTRT or hEST2. The expression of hTRT in human cultured cells is well correlated with telomerase activity and immortality. Moreover, the expression of hTRT in cancer tissues is higher than that of normal tissues. These results suggested that hTRT and telomerase activity may be a powerful **additional** tool for cancer diagnosis.

L5 ANSWER 5 OF 10 MEDLINE on STN
AN 97274210 MEDLINE
TI Reverse transcriptase motifs in the catalytic subunit of telomerase.
SO SCIENCE, **(1997 Apr 25)** 276 (5312) 561-7.
Journal code: 0404511. ISSN: 0036-8075.
AU Lingner J; Hughes T R; Shevchenko A; Mann M; Lundblad V; Cech T R
AB Telomerase is a ribonucleoprotein enzyme essential for the replication of chromosome termini in most eukaryotes. Telomerase RNA components have been identified from many organisms, but no protein component has been demonstrated to catalyze telomeric DNA extension. Telomerase was purified from Euplotes aediculatus, a ciliated protozoan, and one of its proteins was partially sequenced by nanoelectrospray tandem mass spectrometry. Cloning and sequence analysis of the corresponding gene revealed that this 123-kilodalton protein (p123) contains reverse transcriptase motifs. A yeast (Saccharomyces cerevisiae) homolog was found and **subsequently** identified as EST2 (ever shorter telomeres), **deletion** of which had independently been shown to produce telomere defects. Introduction of single amino acid **substitutions** within the reverse transcriptase motifs of Est2 protein led to telomere shortening and senescence in yeast, indicating that these motifs are important for catalysis of telomere elongation in vivo. In vitro telomeric DNA extension occurred with extracts from wild-type yeast but not from est2 **mutants** or **mutants** deficient in telomerase RNA. Thus, the reverse transcriptase protein fold, previously known to be involved in retroviral replication and retrotransposition, is essential for normal chromosome telomere replication in diverse eukaryotes.

L5 ANSWER 6 OF 10 MEDLINE on STN DUPLICATE 4
AN 1998061107 MEDLINE
TI Reconstitution of human telomerase with the template RNA component hTR and the catalytic protein subunit hTRT.
SO NATURE GENETICS, **(1997 Dec)** 17 (4) 498-502.

Journal code: 9216904. ISSN: 1061-4036.

AU Weinrich S L; Pruzan R; Ma L; Ouellette M; Tesmer V M; Holt S E; Bodnar A G; Lichtsteiner S; Kim N W; Trager J B; Taylor R D; Carlos R; Andrews W H; Wright W E; Shay J W; Harley C B; Morin G B

AB The maintenance of chromosome termini, or telomeres, requires the action of the enzyme telomerase, as conventional DNA polymerases cannot fully replicate the ends of linear molecules. Telomerase is expressed and telomere length is maintained in human germ cells and the great majority of primary human tumours. However, telomerase is not detectable in most normal somatic cells; this corresponds to the gradual telomere loss observed with each cell division. It has been proposed that telomere erosion eventually signals entry into senescence or cell crisis and that activation of telomerase is usually required for immortal cell proliferation. In **addition** to the human telomerase RNA component (hTR; reference 11), TR1/TLP1 (refs 12, 13), a protein that is homologous to the p80 protein associated with the Tetrahymena enzyme, has been identified in humans. More recently, the human **telomerase reverse transcriptase** (hTRT; refs 15, 16), which is homologous to the reverse transcriptase (RT)-like proteins associated with the Euplotes aediculatus (Ea_p123), Saccharomyces cerevisiae (Est2p) and Schizosaccharomyces pombe (5pTrt1) telomerases, has been reported to be a telomerase protein subunit. A catalytic function has been demonstrated for Est2p in the RT-like class but not for p80 or its homologues. We now report that in vitro transcription and translation of hTRT when co-synthesized or mixed with hTR reconstitutes telomerase activity that exhibits enzymatic properties like those of the native enzyme. Single amino-acid changes in conserved telomerase-specific and RT motifs reduce or abolish activity, providing direct evidence that hTRT is the catalytic protein component of telomerase. Normal human diploid cells transiently expressing hTRT possessed telomerase activity, demonstrating that hTRT is the limiting component necessary for restoration of telomerase activity in these cells. The ability to reconstitute telomerase permits further analysis of its biochemical and biological roles in cell aging and carcinogenesis.

L5 ANSWER 7 OF 10 MEDLINE on STN

AN 97132577 MEDLINE

TI Senescence **mutants** of Saccharomyces cerevisiae with a defect in telomere replication identify three **additional** EST genes.

SO Genetics, **(1996 Dec)** 144 (4) 1399-412.
Journal code: 0374636. ISSN: 0016-6731.

AU Lendvay T S; Morris D K; Sah J; Balasubramanian B; Lundblad V

AB The primary determinant for telomere replication is the enzyme telomerase, responsible for elongating the G-rich strand of the telomere. The only component of this enzyme that has been identified in Saccharomyces cerevisiae is the TLC1 gene, encoding the telomerase RNA subunit. However, a yeast strain defective for the EST1 gene exhibits the same phenotypes (progressively shorter telomeres and a senescence phenotype) as a strain **deleted** for TLC1, suggesting that EST1 encodes either a component of telomerase or some other factor essential for telomerase function. We designed a multitiered screen that led to the isolation of 22 **mutants** that display the same phenotypes as est1 and tlc1 **mutant** strains. These **mutations** mapped to four complementation groups: the previously identified EST1 gene and three **additional** genes, called EST2, EST3 and EST4. Cloning of the EST2 gene demonstrated that it encodes a large, extremely basic novel protein with no motifs that provide clues as to function. Epistasis analysis indicated that the four EST genes function in the same pathway for telomere replication as defined by the TLC1 gene, suggesting that the EST genes encode either components of telomerase or factors that positively regulate telomerase activity.

L5 ANSWER 8 OF 10 MEDLINE on STN DUPLICATE 5

AN 95059012 MEDLINE

TI Oligonucleotides complementary to the Oxytricha nova telomerase RNA **delineate** the template domain and uncover a novel mode of primer utilization.

SO MOLECULAR AND CELLULAR BIOLOGY, **(1994 Dec)** 14 (12) 7827-38.
Journal code: 8109087. ISSN: 0270-7306.

AU Melek M; Davis B T; Shippen D E

AB The **telomerase reverse transcriptase** uses an essential RNA subunit as a template to direct telomeric DNA synthesis. The 190-nucleotide Oxytricha nova telomerase RNA was identified by using an oligonucleotide probe complementary to the predicted CCCCAAAA template. This RNA displays extensive sequence similarity to the Euplotes crassus telomerase RNA and carries the same 5' CAAAACCCCAAAACC 3' telomeric domain. Antisense oligonucleotides were used to map the boundaries of the functional template and to investigate the mechanism of primer recognition and elongation. On the basis of their ability to inhibit or to prime telomerase, oligonucleotides were classified into three categories. Category 1 oligonucleotides, which extended 5' of residue 42 in the RNA, abolished elongation of (T4G4)3 and (G4T4)3 primers in vitro. In contrast, oligonucleotides terminating between residues 42 and 50 (categories 2 and 3), served as efficient telomerase primers. We conclude that the O. nova template comprises residues 42 to 50 in the 190-nucleotide RNA, a different set of nucleotides than are used by the E. crassus enzyme. Category 2 primer reactions amassed short products, and their abundance could be decreased by altering the 5' sequence of the primer, consistent with the two-primer-binding-site model for telomerase. Category 3 primers generated a bimodal distribution of short and long products, each having a unique elongation profile. The long-product profile is inconsistent with sequence-specific primer alignment. Rather, each primer was extended by the same register of TTTTGGGG repeats, suggesting shuttling to a default position within the template. The parallels between telomerase and RNA polymerase elongation mechanisms are discussed.